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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,661	BERNS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-127* is/are pending in the application.

4a) Of the above claim(s) *99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-98 and 100-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-27-07 has been entered.

Applicants' remark filed on 11-27-07 has been entered. Claims 89-127 are pending. Claims 89-98 and 100-127 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 89-98 and 100-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "flanking sequences that are derived from said inbred strain of animal" in lines 10-11 of claim 89 is vague and renders the claim indefinite. It is unclear what "said inbred strain of animal" refers to. It is unclear whether the phrase "said inbred strain of animal" refers to "an inbred strain of animal" in the beginning of line 2, "an inbred strain of an animal" in lines 2-3, or "an inbred strain of animal" in line 6. Claims 90-98 and 100-127 depend from claim 89 but fail to clarify the indefiniteness.

The phrase "said inbred strain of animal" in claims 96, 97, 115 and 121-124 is vague and renders the claim indefinite. It is unclear what "said inbred strain of animal" refers to. It is unclear whether the phrase "said inbred strain of animal" refers to "an inbred strain of animal" in the beginning of line 2, "an inbred strain of an animal" in lines 2-3, or "an inbred strain of animal" in line 6.

The phrase "derived from" in line 10 of claim 89 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". The specification fails to specifically define the phrase "derived from". The phrase "flanking sequences that are derived from said inbred strain of animal" means during the process of obtaining the flanking sequences, various different modifications on the flanking sequences can happen. Those modifications encompass numerous genetic modifications, chemical modifications, and physical modifications, or their combination thereof. It is unclear what type(s) of modification on the flanking sequences is intended. Claims 90-98 and 100-127 depend from claim 89 but fail to clarify the indefiniteness.

The phrase "derived from" in line 2 of claim 105 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". The specification fails to specifically define the phrase "derived from". The phrase "DNA sequence is derived from cells" means during the process of obtaining the DNA sequence, various different modifications on the DNA sequences can happen. Those modifications encompass numerous genetic modifications, chemical modifications, and physical modifications, or their combination thereof. It is unclear what type(s) of modification on the DNA sequence is intended.

The phrase "said introduction step comprises ..." in claim 112 is vague and renders the claim indefinite. The term "comprises" is an open language, which means other unknown element or component could be included. It is unclear what other introduction step is intended other than the steps recited in the claim.

The phrase "and/or a termination signal" in line 2 of claim 108 is vague and renders the claim indefinite. It is unclear whether "a termination signal" is intended or not.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 89-98 and 100-127 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising modified embryonic stem (ES) cells of an inbred strain of mouse, wherein said modified cells has targeting DNA sequence undergoes homologous recombination with target DNA sequence in the genome of the ES cells in vitro, does not reasonably provide enablement for a composition comprising various modified cells of an inbred strain of animal, wherein said modified cells has targeting DNA sequence undergoes homologous recombination with target DNA sequence in the genome of the target cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are directed to an in vitro composition of cultured cells comprising modified cells of an inbred strain of animal and one or more of unmodified cells of an inbred strain of an animal, progenies of the modified cells and progenies of the unmodified cells, said composition produced by a method comprising introducing a target DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro, wherein said targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of unmodified cells, and said target DNA sequence comprises said at

least one modification sequence and flanking sequences that are derived from said inbred strain of animal. Claim 90 specifies the method further comprises incubating the cells and said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified cells. The modified cells, unmodified cells and their progenies do NOT require integration of targeting DNA sequence into the genome of the cells. Claims 91 and 92 specify the targeting DNA construct is produced in a prokaryotic cell, such as E. coli. Claims 93-95 specify % of modified cells undergo homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence. Claim 98 specifies the modified cells are stem cells, germ cells, or somatic cells. Claims 101-120 specify the structure of the target DNA construct, comprising a coding region, a promoter, a enhancer, a gene that is selectable marker, such as neomycin resistance gene, etc., the length of flanking sequence and % identity of the flanking sequence to the target DNA sequence, method of introducing targeting DNA sequence into the unmodified cells, and modification of the target DNA sequence in the modified cells by insertion, deletion, substitution or combination thereof. Claim 121 specifies the inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse. Claims 122-125 specify the plurality of unmodified cells or the targeting DNA sequence is from substrain of said inbred strain of animal. Claim 126 specifies the at least one modification sequence comprises a nucleic acid that encodes and produces a polypeptide. Claim 127 specifies the at least one modification sequence corrects a defective gene in said target DNA.

The claims encompass using numerous different cells, including different somatic cells, germ cells and ES cells, derived from numerous different inbred strain of animal, such as humans, rats, mice, sheep, horse, dogs, pigs, monkeys, other mammals, birds, fishes etc., to

perform homologous recombination in the genome of the targeted cells. The specification only teaches using mouse ES cells derived from 129 strain for gene targeting via homologous recombination in vitro. The specification fails to provide adequate guidance and evidence for how to use various cell types of somatic cells, germ cells and ES cells derived from numerous different inbred strain of animal for homologous recombination in the genome of said cells.

Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so- called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column).

A search for the embryonic stem cells shows that there are only mouse ES cell available at the time of the invention, i.e. 8-20-91. It is apparent that applicants do NOT have possession of various ES cells derived from any inbred strain of animal other than the inbred strain of mouse. Therefore, the claims are NOT enabled for using various ES cells other than ES cells from inbred mouse strain for homologous recombination in vitro as claimed.

Denning et al., 2003 (Reproduction, Vol. 126, p. 1-11) reports that "until recently, precise modification of the animal genome by gene targeting was restricted to the mouse because germline competent embryonic stem cells are not available in any other mammalian species" and "improvement in the efficiency of somatic cell gene targeting and a greater understanding of the reprogramming events that occur during NT are required for the routine application of what is currently an inefficient process" (e.g. abstract). It appears that the ES cells available for homologous recombination in vitro at the time of the invention are restricted to the mouse ES cells and somatic cell gene targeting via homologous recombination has very poor efficiency. Absent specific guidance and evidence, one skilled in the art at the time of the invention would not know how use the full scope of the claimed cells for gene targeting via homologous recombination in vitro.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 89-98 and 100-127 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Capecchi et al. (IDS, C06-1989).

The claims are directed to an in vitro composition of cultured cells comprising modified cells of an inbred strain of animal and one or more of unmodified cells of an inbred strain of an animal, progenies of the modified cells and progenies of the unmodified cells, said composition produced by a method comprising introducing a target DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro, wherein said targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the

genome of said plurality of unmodified cells, and said target DNA sequence comprises said at least one modification sequence and flanking sequences that are derived from said inbred strain of animal. Claim 90 specifies the method further comprises incubating the cells and said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified cells. The modified cells, unmodified cells and their progenies do NOT require integration of targeting DNA sequence into the genome of the cells. Claims 91 and 92 specify the targeting DNA construct is produced in a prokaryotic cell, such as E. coli. Claims 93-95 specify % of modified cells undergo homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence. Claim 98 specifies the modified cells are stem cells, germ cells, or somatic cells. Claims 101-120 specify the structure of the target DNA construct, comprising a coding region, a promoter, a enhancer, a gene that is selectable marker, such as neomycin resistance gene, etc., the length of flanking sequence and % identity of the flanking sequence to the target DNA sequence, method of introducing targeting DNA sequence into the unmodified cells, and modification of the target DNA sequence in the modified cells by insertion, deletion, substitution or combination thereof. Claim 121 specifies the inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse. Claims 122-125 specify the plurality of unmodified cells or the targeting DNA sequence is from substrain of said inbred strain of animal. Claim 126 specifies the at least one modification sequence comprises a nucleic acid that encodes and produces a polypeptide. Claim 127 specifies the at least one modification sequence corrects a defective gene in said target DNA.

Capecchi teaches a method for producing an alteration in a gene of interest by targeting through homologous recombination. Therefore, during the process of said method, the

intermediate products of different stages of said method would be produced, i.e. mixed population of modified cells and unmodified cells would be produced during the process. Capecchi teaches "[t]hrough gene targeting, the potential now exists to generate mice of any desired genotype. The experimenter chooses both which gene to mutate and how to mutate it. The criteria for selecting which gene to mutate can be based on knowledge generated within the species or from other species" (e.g. p. 70, left column 3rd paragraph). Capecchi teaches that "the application of this approach to mouse genetics is dependent on the availability of a cloned, genomic fragment of the chosen locus. At present this does not appear to be a limitation. The number of available cloned mouse genes that now exist is very large and new methods for isolating additional genes are continually being developed" (e.g. p. 70, right column). Capecchi also teaches that "the frequency of recombination between co-introduced DNA molecules is strongly proportional to the extent of homology between them. When DNA molecules share more than 5 kilobases of homology, then nearly every molecule introduced into cell nucleus participates in at least one recombination event" (e.g. p. 71, left column, top paragraph). Capecchi teaches using PNS vector for altering mouse genome by gene targeting via homologous recombination (e.g. p. 74-75).

The term "homology" implies similarity between sequences and encompasses 100% identity. As pointed out in the cited Reeck reference filed on 11-27-07, the term "homology" has the precise meaning in biology of "having a common evolutionary origin", but it also carries the loose meaning of "possessing similarity or being matched" (p. 667, left column). Although Capecchi does not specifically teach 100% identity between the targeting DNA flanking sequence and the target DNA sequence in the genome of the cells, one of ordinary skill in the art

would envision that the higher similarity, including 100% identity, between two DAN sequences the higher frequency of recombination between these two DNA sequences would be after reading the phrase by Capecchi "the frequency of recombination between co-introduced DNA molecules is strongly proportional to the extent of homology between them. When DNA molecules share more than 5 kilobases of homology, then nearly every molecule introduced into cell nucleus participates in at least one recombination event".

Further, it should be noted that as discussed above under 35 U.S.C. 112 second paragraph, the phrase "derived from" in line 10 of claim 89 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". The phrase "flanking sequences that are derived from said inbred strain of animal" does not mean that the flanking sequences are 100% identical to the corresponding sequence in the target DNA sequence of genome. Thus, the claims are anticipated by Capecchi.

Although Capecchi does not specifically teach % of unmodified cells undergoing homologous recombination, the length of the flanking sequences, the % identity of the flanking sequences and the inbred strain of 129 or BALB/c strain of mouse, the teachings of Capecchi would encompass various % of homologous recombination, the length of flanking sequence and its % identity. In the event that those features are not anticipated by Capecchi, it would be obvious to one of ordinary skill in the art at the time of the invention in order to optimize the frequency of the homologous recombination between the targeting DNA sequence and the target DNA sequence in the genome, and the strains of 129 and BABL/c mouse were well known in the art at the time of the invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 89-98, 100-120 and 122-127 are rejected under 35 U.S.C. 102(e) as being anticipated by Capecchi et al. (US Patent No. 5,464,764).

The claims are directed to an in vitro composition of cultured cells comprising modified cells of an inbred strain of animal and one or more of unmodified cells of an inbred strain of an animal, progenies of the modified cells and progenies of the unmodified cells, said composition produced by a method comprising introducing a target DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro, wherein said targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of unmodified cells, and said target DNA sequence comprises said at least one modification sequence and flanking sequences that are derived from said inbred strain of animal. Claim 90 specifies the method further comprises incubating the cells and said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified cells. The modified cells, unmodified cells and their progenies do NOT require integration of targeting DNA sequence into the genome of the cells. Claims 91 and 92 specify the targeting DNA construct is produced in a prokaryotic cell, such as E. coli.

Claims 93-95 specify % of modified cells undergo homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence. Claim 98 specifies the modified cells are stem cells, germ cells, or somatic cells. Claims 101-120 specify the structure of the target DNA construct, comprising a coding region, a promoter, a enhancer, a gene that is selectable marker, such as neomycin resistance gene, etc., the length of flanking sequence and % identity of the flanking sequence to the target DNA sequence, method of introducing targeting DNA sequence into the unmodified cells, and modification of the target DNA sequence in the modified cells by insertion, deletion, substitution or combination thereof. Claims 122-125 specify the plurality of unmodified cells or the targeting DNA sequence is from substrain of said inbred strain of animal. Claim 126 specifies the at least one modification sequence comprises a nucleic acid that encodes and produces a polypeptide. Claim 127 specifies the at least one modification sequence corrects a defective gene in said target DNA.

Capecchi teaches a method for homologous recombination events between DNA sequences residing in the genome of a cell or organism and newly introduced DNA sequences for systematically altering the genome of the cell or organism and to overcome problems associated with random integration involves the use of gene targeting (e.g. column 2, lines 35-41). Capecchi teaches positive-negative selector (PNS) vectors containing a first DNA sequence which contains at least one sequence portion which is substantially homologous to a portion of a first region of a target DNA sequence, and a second DNA sequence containing at least one sequence portion which is substantially homologous to another portion of a second region of a target DNA sequence for homologous recombination in cells. The PNS vectors can contain a third DNA sequence containing a positive selection marker under the control of a regulatory

region for expression and can be positioned within an intron in a eukaryotic gene, such that modification of surrouding target sequence by wasy of substitution, insertion and/or deletion of one or more nucleotides may be made without eliminating the functional character of the target gene (e.g. column 5-6, Figure 3). "Substantial homology is necessary between these portions in the PNS vector and the target DNA to insure targeting of the PNS vector to the appropriate region of the genome" and Figure 4 compare absolute frequency of homologous recombination and the amount of 100% sequence homology in the first and second DNA sequences of the PNS vectors (e.g. column 6, lines 55-58, Figure 4). Modified DNA sequences contain the substitution, insertion and/or deletion of one or more nucleotides in a first transformed target cell modified by a PNS vector (e.g. column 10, lines 43-54). Capecchi also teaches using neo marker gene in the PNS vector to target X gene via homologous recombination (e.g. column 12, lines 12-16). Capecchi teaches that in the PNS vector "the first DNA sequence comprises part of exon I and a portion of a contiguous intron in the target DNA. The second DNA sequence encodes an adjacent portion of the same intron and optionally may include all or a portion of exon II" (e.g. column 13, lines 37-42). It appears that the first and second DNA sequences in the PNS vector are exactly the same as the corresponding sequences in the target DNA. The PNS vectors can be efficiently introduced into the ES cells by electroporation or microinjection or other transformation methods (e.g. bridging columns 15-16). PNS vector can be used in gene therapy to correct genetic defect, such as sickle cell anemia (e.g. column 16, lines 11-33). Capecchi teaches inactivation at the int-2 locus in mouse ES cells via homologous recombination between PNS vector and genomic sequence in mouse ES cells (e.g. Example 1).

The term "homology" implies similarity between sequences and encompasses 100% identity. As pointed out in the cited Reeck reference filed on 11-27-07, the term "homology" has the precise meaning in biology of "having a common evolutionary origin", but it also carries the loose meaning of "possessing similarity or being matched" (p. 667, left column). Although Capecchi does not specifically teach 100% identity between the targeting DNA flanking sequence and the target DNA sequence in the genome of the cells, the phrase "100% sequence homology" implies 100% sequence identity.

Further, it should be noted that as discussed above under 35 U.S.C. 112 second paragraph, the phrase "derived from" in line 10 of claim 89 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". The phrase "flanking sequences that are derived from said inbred strain of animal" does not mean that the flanking sequences are 100% identical to the corresponding sequence in the target DNA sequence of genome. Thus, the claims are anticipated by Capecchi.

Applicants cite Dr. Anton Berns's declaration and argue that at the time of the invention, the scientist generally expected that increasing the length of the homologous region would increase the efficiency of gene targeting, however, the increase in efficiency is not related to the degree of sequence identity, and Capecchi's teachings fail to say anything about how to use the flanking sequences of the targeting DNA construct and the target cells. Applicants further argue that the term "extent of homology" does not refer to nucleotide sequence identity rather it refers to the length of the homologous region (remark, p. 7-9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102/103 rejection and 102(b) rejection. The phrase "derived from" in line 10 of claim 89 is vague and renders the claim indefinite. It is unclear as to

the metes and bounds of what would be considered "derived from". The phrase "flanking sequences that are derived from said inbred strain of animal" can be interpreted to mean that the flanking sequences are not necessarily 100% identical to the corresponding sequence in the target DNA sequence of genome. Further, although Capecchi does not specifically teach 100% identity between the targeting DNA flanking sequence and the target DNA sequence in the genome of the cells, the phrase "100% sequence homology" implies 100% sequence identity. Although the term "homologous recombination" means that the sequences that recombine need only be homologous to each other, however, Capecchi teaches that "substantial homology is necessary between these portions in the PNS vector and the target DNA to insure targeting of the PNS vector to the appropriate region of the genome" and one of ordinary skill would understand that the higher the homology the better the homologous recombination would be, and the phrase "100% sequence homology" implies 100% sequence identity.

Applicants argue that the invention requires the flanking sequences of the targeting DNA construct and the targeted cells are from the same inbred strain of animal, and at the time of the invention, the scientist would not have the motivation to take special steps involving considerable time, effort and expense to use targeting DNA and targeted cells from the same inbred strain for gene targeting (remark, p. 9-11). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102/103 rejection and 102(b) rejection, and the reason set forth above.

Applicants cite Reeck reference and argue that the precise biological meaning of "homology" is a concept of quality, and the phrase "100% sequence homology" cited in Capecchi ('764) simply means that they are from same species not strain. Applicants cite

Capecchi 1989 (Exhibit C) and Thomas 1987 (Exhibit D) and argue that the Hprt sequence and ES cells are derived from different mouse strains, and the phrase "100% sequence homology" in brief description of Figure 4 only describes an evolutionary relationship and not likely to mean 100% identical (remark, p. 11-13). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102/103 rejection and 102(b) rejection, and the reason set forth above. It is unclear where in the cited Capecchi 1989 (Exhibit C) refers back to Thomas 1987 (Exhibit D) regarding the sequence of Hprt and the origin of the ES cells. In fact, the cited reference Capecchi 1989 (Exhibit C) states "the word "homology" is used here to describe participants in homologous recombination, which are generally identical). Over the range tested, from 2.9 to 14.3 kb, a fivefold increase in DNA sequence homology resulted in roughly a 100-fold increase in the targeting frequency" (e.g. p. 1289, right column, 1st full paragraph, this paragraph refers to Figure 3 of Exhibit C, which is the same as Figure 4 of '764). It appears that the higher the homology or identity the sequences have, the higher the targeting frequency would be. Thus, the phrase "100% sequence homology" in brief description of Figure 4 implies "100% sequence identity".

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 89, 90 and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al. (US Patent No. 5,464,764) in view of Koller et al. (US Patent No. 5,416,260).

The claims are directed to an in vitro composition of cultured cells comprising modified cells of an inbred strain of animal and one or more of unmodified cells of an inbred strain of an animal, progenies of the modified cells and progenies of the unmodified cells, said composition produced by a method comprising introducing a target DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro, wherein said targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of unmodified cells, and said target DNA sequence comprises said at least one modification sequence and flanking sequences that are derived from said inbred strain of animal. Claim 90 specifies the method further comprises incubating the cells and said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified cells. The modified cells, unmodified cells and their progenies do NOT require integration of targeting DNA sequence into the genome of the cells. Claim 121 specifies the inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse.

The teaching of Capecchi is as discussed above.

Capecchi does not specifically teach cells from inbred 129 strain or BALB/c strain of mouse.

Koller teaches the use of mouse ES cell line E14TG2a, which was isolated from strain 129/01a embryos, as targeted ES cells for the production of chimeric or transgenic mice via homologous recombination (e.g. column 13, 14).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use ES cells isolated from 129 strain of mouse as targeted cells for homologous recombination in said targeted cells because Capecchi teaches using mouse ES cells for gene targeting via homologous recombination and Koller teaches using ES cells isolated from 129/01a strain embryo for production of chimeric or transgenic mice via homologous recombination.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order for gene targeting via homologous recombination as taught by Capecchi or for production of chimeric or transgenic mice via homologous recombination as taught by Koller with reasonable expectation of success.

15. Claims 89-98 and 100-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al. (IDS, C06-1989) or Capecchi et al. (US Patent No. 5,464,764) each in view of Doetschman et al., 1987 (Nature, Vol. 330, p. 576-578, IDS-C14).

The claims are directed to an in vitro composition of cultured cells comprising modified cells of an inbred strain of animal and one or more of unmodified cells of an inbred strain of an animal, progenies of the modified cells and progenies of the unmodified cells, said composition

produced by a method comprising introducing a target DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro, wherein said targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of unmodified cells, and said target DNA sequence comprises said at least one modification sequence and flanking sequences that are derived from said inbred strain of animal. Claim 90 specifies the method further comprises incubating the cells and said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified cells. The modified cells, unmodified cells and their progenies do NOT require integration of targeting DNA sequence into the genome of the cells. Claims 91 and 92 specify the targeting DNA construct is produced in a prokaryotic cell, such as E. coli. Claims 93-95 specify % of modified cells undergo homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence. Claim 98 specifies the modified cells are stem cells, germ cells, or somatic cells. Claims 101-120 specify the structure of the target DNA construct, comprising a coding region, a promoter, a enhancer, a gene that is selectable marker, such as neomycin resistance gene, etc., the length of flanking sequence and % identity of the flanking sequence to the target DNA sequence, method of introducing targeting DNA sequence into the unmodified cells, and modification of the target DNA sequence in the modified cells by insertion, deletion, substitution or combination thereof. Claim 121 specifies the inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse. Claims 122-125 specify the plurality of unmodified cells or the targeting DNA sequence is from substrain of said inbred strain of animal. Claim 126 specifies the at least one modification sequence comprises a

nucleic acid that encodes and produces a polypeptide. Claim 127 specifies the at least one modification sequence corrects a defective gene in said target DNA.

This 103(a) rejection is applied in the event that the phrase "flanking sequences that are derived from said inbred strain of animal" is interpreted as that the flanking sequences in the targeting DNA construct are exactly the same as the corresponding sequences in the genome of target cells and both are from same inbred strain, and the phrase "100% sequence homology" is not interpreted as "100% sequence identity".

The teachings of Capecchi (1989) and Capecchi ('764) are as discussed above.

Capecchi does not specifically teaches using flanking sequences in the targeting DNA construct that are 100% identical to the corresponding sequences in the genome of target cells.

Doetschman teaches "homologous recombination between a target chromosomal locus and exogenous DNA having sequences in common with the target" and using correcting plasmid, pNMR133, to correct the deletion in the HPRT gene of the ES cell line E14TG2a, wherein the pNMR133 vector has between 2.5 and 5kb of DNA in common with the target locus (e.g. p. 577, left column, Figure 1). The phrase "has between 2.5 and 5kb of DNA in common with the target locus" is considered that the flanking sequences in the plasmid (2.5 and 5kb) are the same or 100% identical to the corresponding sequences in the target locus.

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use flanking sequences in the targeting DNA construct that are 100% identical to the corresponding sequences in the target locus of ES cells because Doetschman teaches using correcting plasmid, pNMR133, to correct the deletion in the HPRT gene of the ES cell line

E14TG2a, wherein the pNMR133 vector has between 2.5 and 5kb of DNA in common with the target locus.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to correct the deletion in the HPRT gene of the mouse ES cells via homologous recombination as taught by Doetshman with reasonable expectation of success.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 89-98 and 100-127 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,653,113. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the claims.

18. Claims 89-98 and 100-127 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,789,215. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the claims.

Applicants' indication of submitting a Terminal Disclaimer under 37 C.F.R. 1.321(c) upon indication of allowable subject matter is acknowledged.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER